Introduction

“Psychosis” is an abnormal condition of the mind that involves a "loss of contact with reality". People experiencing psychosis may exhibit personality changes and thought disorder. Psychosis can lead to changes in mood and thinking and to abnormal ideas. In order to understand the experience of psychosis, it is associated with confused thinking, false beliefs (delusions), hallucinations and changed feelings with poor emotions (Morgan et al. 2011). The characteristics of psychosis varied from person to person considering their mental status and surrounding environment. Sometimes, psychosis may be induced by extreme use or withdrawal of drugs (including drugs of abuse), head injury or a physical illness (organ psychosis which disrupts brain functioning), traumatic stress, unplanned pregnancy, sudden demise of beloved person etc. (EPPIC Information sheet, 2006). There are several forms of psychotic illness which are associated to major brain disorders like Schizophrenia, Bipolar disorder (sometimes refer to mood disorder), Schizoaffective disorder (symptoms of both mood disorder and schizophrenic state), Psychotic depression (major depression with psychotic symptoms). Furthermore, hormonal fluctuations, emotional stress and other factors such as personal and social changes in the women set them on stage of psychosis (Carey, 2016).

Prevalence of psychosis or psychiatric disorders ranged from 0.8% to 31.4% in general population who have experienced with psychotic episode at some point in their life (Nuevo et. al., 2010). Literature also revealed that among the prevalence of psychotropic disorders, anxiety ranked first (~18.2%), followed by mood disorders (~9.6%) and substance disorders (~6.4%). WHO (2016) documented that Schizophrenia is a severe mental disorder affecting more than 21 million people worldwide. The
prevalence of psychosis is higher in women than in man in the world population including India (Sundquist et al., 2004).

The prevalence of psychiatric disorders in pregnancy ranged from 14% to 30.5 % (Andersson et al., 2003; Lee et. al., 2007; Melville et. al., 2010; Alessandra et. al., 2016). It is well documented that untreated psychiatric disorders during pregnancy are associated with increased risks of adverse pregnancy outcomes, and sometimes may affect pregnant mother and developing foetuses, concomitantly. Hence, there is need to select a suitable antipsychotic drug (APD) and decide the treatment regime and exposure period.

Antipsychotic drugs were discovered in the 1950s and currently over 20 compounds available and mostly approved by USFDA (WHO 2016). For therapeutic management of vivid forms of psychosis several antipsychotic agents belong to diverse classes first-generation (classical or typical), second-generation (atypical) and third-generation (novel) are available in the global market (Hippius, 1989; Meltzer et al., 1989; Leucht et al., 2009). The typical or conventional antipsychotics drugs (APDs) like haloperidol and chlorpromazine are the best known classical antipsychotics. They continue to be useful in the treatment of severe psychosis and behavioural problems. However, these medications perform a high risk of side effects, some of which are quite severe. In response to serious side effects of typical antipsychotics, many second-generation antipsychotic drugs were developed as another category and referred to as atypical antipsychotics drugs (AAPDs). These new medications like clozapine, amisulpride, risperidone, sertindole, olanzapine, quetiapine, ziprasidone, paliperidone, iloperidone and brexpiprazole etc. were made available for pharmacological management of psychosis. Aripiprazole is a relatively new approved antipsychotic drug and classified as third generation or novel
antipsychotic drug on the basis of their unique mechanism of action (Lieberman, 2004).

Antipsychotics such as typical antipsychotic drugs (APDs) like haloperidol and chlorpromazine tend to block dopamine D2 receptors in the dopaminergic pathways of the brain (Pickar et al., 1990; Schmidt et al., 1995). In addition to the antagonistic effects of dopamine, second generation or atypical antipsychotics drugs (AAPDs) like quetiapine, risperidone and iloperidone etc. also antagonize serotonin (5-HT2A) receptors (McDonald and Murphy, 2003; Schmidt et al., 1995). The distinction between second- and third-generation antipsychotics has been made based on mechanistic differences. Specifically, aripiprazole (ARI) is the first approved antipsychotic that is a partial dopamine agonist and has been designated as a third-generation antipsychotic. It’s mechanism of action is unique, compared to other FDA approved atypical antipsychotic drugs. It is partial agonist at D2 and 5HT1A receptors, but displays an antagonist profile at the 5HT2A receptors. ARI also antagonise the 5HT7 receptors and act as partial agonist at the 5HT2c receptor with high affinity. Most atypical antipsychotic bind preferentially to extrastriatal receptors, but ARI appears less preferential, as binding rates are high throughout the brain (Potkin et al., 2003; Guzman, 2016).

It is well documented that first-generation APDs (typical) are associated with stereotypic side effects like extrapyramidal syndrome (EPS) and movement disorders. The reproductive toxicity and teratogenicity of first-generation APDs has been well established in clinical and non-clinical studies (Nevena and Milica, 2014; Correll, 2014). Therefore, clinicians vacillate to prescribe typical antipsychotics to the pregnant women with psychosis considering teratogenic potential of classical APDs. Some investigators have revealed the effect of typical antipsychotics
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antipsychotics like haloperidol (HAL) on developmental structural changes in fetal brain whose mothers had taken either single (monotherapy) or multiple APDs (polytherapy) during first, second or third-trimester of pregnancy or throughout gestation period. Similar studies were also reported in rodent models (Singh and Singh, 2001, 2002; Zhang et al., 1996).

During past two decades, several atypical antipsychotics (AAPDs) like clozapine, olanzapine (OLZ), ziprasidone, quetiapine (QUE), risperidone (RIS) and iloperidone (ILO) were launched in the world market to treat different forms of psychosis in young and adult population with different mechanism of action than typical APDs, but drug safety in the pregnant population was not well established in clinical settings due to paucity of accumulating data. Although general safety concerns of antipsychotics have been improved enormously from development of classical APDs to novel AAPDs, including their efficacy, pharmacokinetics and pharmacodynamic; and drug interactions, but none of the drug has been found to be safer for treatment of pregnant population suffering from psychosis (Newharm et al., 2008; McKenna et al. 2005; Coppola et al. 2007).

The second-generation antipsychotic drugs (AAPDs) like clozapine, olanzapine, ziprasidone, quetiapine (QUE), risperidone (RIS) and iloperidone (ILO) show low incidence of extrapyramidal side effects (EPS) than APDs due to their low affinity for D2 receptors and antagonistic characteristics of 5HT2 receptors (Panoriello et al., 2012; De Fruyt et al., 2012). Although reproductive and teratogenic safety of AAPDs has been improved to a great extent than classical antipsychotic drugs (APDs) like haloperidol, but literature (clinical and non-clinical) indicates that second-generation APDs are coupled with metabolic dysregulation, especially the weight gain. However, increased weight gain, obesity, diabetes mellitus, hyperglycemia,
hypertension, osteoarthritis and lipid abnormalities are the common side effects associated with long-term treatment of AAPDs (Panoriello et al., 2012; Ferano et al., 2011). Among the major side effects of AAPDs, weight gain is the main concern for metabolic disorder.

AAPDs induce marked weight gain as a side effect which is associated with increased morbidity, mortality and reduced quality of life (Goudie et al., 2005; Ucok et al., 2008). In adults, nearly all AAPDs are associated with weight gain (26–55%) in humans depending upon drug doses and exposure period (Goudie et al., 2005; Allision et al., 2001). The greatest increases in body weight have been observed with clozapine followed by olanzapine and risperidone treatment (Allision et al., 2001). The magnitude of weight gain, however, varies between drugs due to their mechanism of action.

The clinical literature revealed that olanzapine (OLZ) is associated with excessive weight gain in schizophrenic patients with prolonged therapy (Lambert et al., 2005; Duggan et al., 2005), whereas quetiapine (QUE) may cause mild body weight gain (Brecher et al., 2000; Shaw et al., 2004), and risperidone (RIS) designated as neutral in weight gain (Singh et al., 2014). Thus, selection of second-generation AAPDs among all available atypical agents is an alternate option to treat the pregnant women after weighing the balance between potential benefits to pregnant mother and risks to developing fetus, respectively. Hence, RIS could be a better alternative for pregnant women with psychosis.

Reports on iloperidone (ILO) induced weight gain are also inconclusive and somewhat contradictory in clinical and preclinical trials. While some studies suggest the lowest weight gain potential with relevant short-term metabolic effects for asenapine and iloperidone (Hert et al., 2012), data are still too sparse to
comprehensively evaluate the metabolic safety of the newly approved AAPDs. The product monograph revealed that prenatal exposure to ILO displayed decrease in maternal body weight gain and food intake in rodents (Product monograph of FDA, 2009). Therefore, there is a clear need for further controlled studies to evaluate whether ILO exposure is less problematic regarding treatment-emergent weight gain and metabolic disturbances than other currently available antipsychotics.

In the past decade, use of atypical antipsychotic drugs (AAPDs) has been drastically increased in the pregnant women with psychiatric disorders including schizophrenia and bipolar disorder (Littrell et al., 2000; Mckenna et al., 2004; Trixler et al., 2005). Epidemiological studies documented that use of atypical antipsychotic drugs (AAPDs) has been increased from 16.6 to 51.2% during 1998 to 2007 (Prah et al., 2012). Among the SGAPDs, olanzapine (OLZ) ranked first, followed by quetiapine (QUE) and risperidone (RIS) for their use during pregnancy (Paschetta et al., 2014; Sadwaski et al., 2013). Thus, use of these drugs in pregnant women is increasing as add-on therapy or alternative drugs of choice (Strigler et al., 2004).

Earlier, some studies revealed that prenatal exposure to typical APDs may induce adverse effects on fetal brain development, neurostructural morphology and neurobehavioural changes in later life of humans and animals (Holoson, 1994; Zhang, 1996; Singh and Singh, 2001; 2002). Williams et al., 1992 reported that HAL was administered during gestation period displayed altered structural and cytoarchitectural changes as well as substantive deficit of neuronal density in fetal brain. Some investigators have also reported decreased neuronal cell packing density, increased in neuronal size (synaptic plasticity) in the striatum and striatal enlargement when APDs were administered during prenatal period in rats (Pakkenberg et al., 1973; Nielsen and Lyon, 1978; Chakos et al., 1994; Jeste et al., 1992).
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Despite tremendous increase in the prescription of AAPDs to pregnant population, developmental toxicity and developmental neurotoxicity of AAPDs has not been well documented in clinical and non-clinical studies due to paucity of data. Although, some studies are available on \textit{in utero} exposure to AAPDs and fetal brain development and histopathological alterations, but are scattered, sketchy and inconclusive.

Furthermore, studies are very limited on neurohistopathological changes in fetal brain caused by maternal exposure to AAPDs in general and RIS in particular, whereas reports on prenatal exposure to iloperidone (ILO) and brain development are almost negligible. Earlier, our laboratory (Neurobiology lab.) has reported developmental neurotoxic potential of some CNS acting drug classes like antipsychotics; risperidone (Singh and Singh, 2017; Singh et al, 2016), quetiapine (Singh and Tripathi, 2015, 2014) and aripiprazole (Tripathi, 2015); haloperidol (Singh and Singh, 2002), antidepressant; venlafaxine (Singh et al., 2015; Singh, 2014); antiepileptics; gabapentin and sodium valproate (Singh and Gupta, 2014) and their effects on developing brain.

Additionally, limited information is available on effects of \textit{in utero} administration to AAPDs on postnatal development and growth; and neurobehavioral consequences in young/adult rodent offspring. The clinical and non-clinical studies on these issues are very limited (Newport et al., 2007; McKenna et al., 2005; Coppola et al., 2007). Limited information is available on neurobehavioural consequences (cognitive impairment) in rodents to draw a definite conclusion (Green et al., 2002; Rosengarten and Quartermain, 2002; Karl et al., 2006; Zuo et al., 2008). Recently, our laboratory has reported developmental neurotoxic and neurobehavioural potential of quetiapine, aripiprazole and
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risperidone in fetuses and young rat offspring, respectively (Singh and Tripathi, 2014, 2015; Singh et al, 2016; Singh and Singh, 2017).

Although some literature is available on effects of administration to ILO and neurobehavioral changes in adult rat (Alasdair et al., 2006) which displayed reduced sensory-motor gating deficits in pharmacological models, but not in the prenatal/developmental model in rodents. For iloperidone no clinical data on cognitive functions are presently available. To the best of our knowledge none of the study is available on the prenatal exposure to ILO on neurobehavioral sequelae in rat offspring.

Therefore, health care providers always have a dilemma for selection of safe and efficacious novel antipsychotic drug for therapeutic management of pregnant women suffering from different forms of psychiatric disorders, considering drug safety concerns for potential benefits to diseased mother and possible risks to developing foetus, respectively.

Despite better efficacy and improved pharmacokinetic and pharmacodynamic properties of RIS and ILO in respect to in utero exposure and its safety concerns, as well as paucity of literature on fetal brain development; and long-lasting impact on neurobehavioral consequences, the present study has been undertaken to elucidate the effects of prenatal exposure to RIS and ILO, at equivalent therapeutic doses, on maternal toxicity (food consumption and body weight gain), placental toxicity, reproductive toxicity and teratogenicity, fetal toxicity, developmental neurotoxicity (neocortex, hippocampus, striatum and choroid plexus in fetal brain), postnatal development & growth, and neurobehavioural toxicity (anxiety, depressive and cognitive impairment) in young rat offspring, as translational approach.
Aims & Objectives

Following aims and objectives were undertaken for the present study:

1. Assessment of maternal toxicity as food intake and body weight gain during gestational exposure to RIS and ILO.
2. Evaluation of reproductive and fetal toxicity as well as teratogenic potential of RIS and ILO.
3. Observation of neurohistopathological alterations in different brain regions of rat fetuses such as cortex, striatum and hippocampus.
4. In situ detection of drug induced neuronal apoptosis in selected fetal brain regions by confocal and electron microscopy.
5. Study of postnatal development and growth pattern of prenatally RIS and ILO exposed offspring.
6. Assessment of long-lasting impact of in utero exposure to RIS and ILO on neurobehavioral impairment in young-adult rat offspring under different paradigms of anxiety, depression and cognition.